Synthetic Biology: Applications and Lessons Learned in the Field of Bio-based Materials and Chemicals

Over the past decade, the use of synthetic biology (or "synbio") tools fueled the development of a wide variety of technologies to convert biomass and other non-petroleum feedstocks into chemicals and materials. Advances in sequencing and synthesis enabled companies to scale up and put products out on the market. For those looking to enter or expand their presence in the industrial biotechnology space, the lessons learned from the first waves of Bio-based Material and Chemical companies offer valuable insights for planning future endeavors. This report quantifies and analyzes the scale-up timelines seen in the industry. From there, the lessons learned from the first wave of scale-ups are applied to today's youngest startups – those at lab and pilot scale – to predict the likelihood of each company launching a product in each of the upcoming years.

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Executive Summary

Synthetic biology is now a common tool utilized by large and small players, alike, in the bio-based materials and chemicals space. Advances in sequencing and synthesis enabled companies such as Amyris and Metabolix to scale up and put products out on the market, with another wave of startups looking to scale products ranging from squalane, to malonic acid, and isobutene. In looking at the companies employing synthetic biology to develop industrial processes for bio-based materials and chemicals (BBMC), we found that:

- Data on 23 companies in the BBMC space suggest the industry takes on average 4.70 years, ± 1.92 years, to reach pilot scale from the time of a company's or project's inception. The three companies that reached pilot scale in the shortest amount of time – Nucelis, Reverdia, and Isobionics – all have parent companies with past successes in the industrial biotech space.
- Companies hit commercial scale in roughly 6.20 years from inception, ± 3.03 years if they scale straight from pilot. For those processes that need an intermediate demonstration scale, the average time to commercial scale bumps up by 4.47 years, bringing the average to 10.67 years from inception, ± 4.13 years. Key outliers were Isobionics (three years), AMSilk and Reverdia (five years), and Metabolix (18 years).
- For the 12 companies analyzed with products on the market, the average time it took to put out their first internally developed product was 7.42 years, ± 2.91 years from the time of the company's founding or the project's inception. Three out of the five companies that were the fastest launch products – AMSilk, Allylix (which was later acquired by Evolva), and Genomatica – did so with the use of contract manufacturers.

Using the average values and standard deviations for key scale-up milestones, we ran Monte Carlo analyses to predict the probability that each of today's youngest companies – those currently at lab scale and pilot scale – will put out a product in each of the upcoming years. From there, we analyzed each company relative to past progress, strategy, and upcoming milestones and found that:

- For the youngest startups, first products are most likely to be launched from 2017 to 2022. Yet within that group there are some firms set to scale and launch faster. Nucelis aims to launch its first product, squalane, in Q4 2015, several years ahead of the industry average that would put peak likeliness for product launch between 2019 and 2020. After achieving pilot scale in 2014, Lygos aims to hit demonstration scale in 2015, putting it on track to meet the industry's average for a product launch.
- For those nearing their peak likelihood for product launch, near-term announcements are key milestones to watch for. For companies like Oakbio that continue to develop lab-scale platforms and intend to scale in conjunction with partners, monitor for continued momentum through partnership announcements. For companies like Global Bioenergies that have announced multiple lab- and pilot-scale achievements, monitor for additional scale-up accomplishments – in the case of Global Bioenergies, the next major milestone to look for is the construction of its second industrial isobutene pilot plant, currently set for Q2 2015.

While each company's path is unique, the lessons learned from the first wave of BBMC scale-ups and product launches provide valuable insight and lessons. Today's start-ups still have years to go, but by looking at the results of the Monte Carlo analysis relative to each company's current situation, we get an early indication of which companies are ahead of the curve and which are behind.

Landscape

On average, companies leveraging synthetic biology tools in the BBMC field should expect a gap of 7.42 years, ± 2.91 years, between a project's start and the release of a first product.

Synthetic Biology Grows from a Lab-based Initiative to a Key Tool in Industrial Biotech

Over the past decade, the use of synthetic biology (or "synbio") tools fueled the development of a wide variety of technologies to convert biomass and other non-petroleum feedstocks into chemicals and materials. Advances in sequencing and synthesis enabled companies such as Amyris and Metabolix to scale up and put products out on the market. Though somewhat intangible at times as the field is still evolving, the term synthetic biology can generally be defined as the discovery, invention, and manufacture of biochemical elements and systems to produce tools, materials, organisms, and devices that meet human needs (see the report "Synthetic Biology's Commercial Roadmap").

The types of tools and modifications vary, with companies like Direvo focused on mutagenesis and screening methods, while others like Ascenix Biotechnologies and Genomatica take a computational approach to design. The end result is a microorganism with engineered pathways to produce target molecules either through the insertion of foreign genes (e.g., Amyris and Lygos) – or through non transgenic gene editing (e.g., Nucelis).

Synbio-enabled products are already commercially available, touching markets ranging from pharma, to personal care, lubricants, sweeteners, animal feed, and more. For those companies looking to apply or expand their use of synbio, the practical applications and lessons learned from the startups applying synbio approaches to produce bio-based materials and chemicals (BBMC) products yield many valuable lessons that can be applied to future projects and investments.

Though the term "synbio" encompasses the technical aspects of both the sequencing/synthesis of custom genetic material and the subsequent industrial biotechnology behind the large-scale use of these novel microbes, the term is still somewhat contentious within the industry. During the research for this report, more than one company expressed unease over the use of the term synbio, citing concerns that consumers may be concerned about the use of genetically modified organisms (GMOs) and a general concern that the term is overly technical. Despite concerns related to branding, this report will use the term to describe the set of tools used to bioengineer the microbes used by a variety of companies, both small and large, in the BBMC field.

An Analysis of the Industry's Scale-up Timelines Offers Insight for Future Project Planning

In order to analyze the practical aspects of leveraging synthetic biology for industrial biotech, we looked at the broader BBMC space determine the timelines from project inception to key scale-up milestones: pilot scale, demonstration ("demo") scale, commercial scale, and first product launch. For the sake of the scale-up timeline analysis, the product lines considered needed to be announced, internally developed, and targeting BBMC markets. Because of this, companies putting out products targeting the food and nutrition markets (e.g., Evolva and its stevia product) and companies that have nearer term routes that were acquired (e.g., Calysta's aquacultural feed route that came from the acquisition of BioProtein) are excluded.

One other note on the scope of this report is that the capacity definitions for pilot scale, demo scale, and commercial scale are fluid. In the industry, standard plant sizes can vary drastically depending on the process and target end use markets, as each scale is designed for a specific purpose. Pilot-scale facilities are sized to require low capital investment while providing the data to demonstrate a process is robust and scalable and demo-scale facilities further buydown scale-up risk, while producing material for applications development. Finally, commercial facilities are sized to meet demand and

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Figure 1: Time to Pilot Scale from the Company's or Project's Inception

Number of Years to Pilot Scale	Company Name	One-liner	Primary Product	Current Scale
1	Nucelis	DNA modification for herbicide and disease resistance in crops	Squalane	Pilot
	Reverdia	Manufacturing succinic acid with low-pH process	Succinic acid	Commercial
2	Isobionics	Producing terpenoid derivatives for fragrances, flavorings, and specialty chemicals	Terpenes	Commercial
3	AMSilk	Modified *E. coli* to produce synthetic spidersilk	Spidersilk	Commercial
	Gevo	Biosynthetic production of isobutanol for chemicals and fuels	Isobutanol	Commercial
	LS9 (purchased by Renewable Energy Group)	Synthetically engineered microbes for renewable fuels and chemicals from sugars	C8 to C22 chemicals	Demo
4	MetabolicExplorer	Engineered organisms to produce specialty chemicals such as PDO and propyleneglycol	1,3 propanediol (PDO)	Pilot
	Lygos	Synthetic biology and metabolic engineering routes to renewable chemicals	Malonic acid	Pilot
5	Amyris	Engineering microbes to produce farnesene and specialty chemicals	Farnesene, squalane, artemisinin	Commercial
	BioAmber	Biosynthetic production of succinic acid and derivatives from renewable feedstocks	Succinic acid	Commercial(planned)
	Direvo	Develops enzymes and microorganisms to produce chemicals and improve existing processes	Lactic acid	Pilot
	Genomatica	Bio-based process technology for the production of multiple major chemicals	BDO	Commercial
	Industrial Technology Research Institute / ITRI	Itaconic acid through bacterial fermentation	Itaconic acid	Pilot
	MetabolicExplorer	Engineered organisms to produce specialty chemicals such as PDO and propyleneglycol	Monopropylene glycol (MPG)	Pilot
	Photanol	Engineers cyanobacteria to convert CO_2 to terpenes, chemicals, and biofuels	Terpenes	Pilot
	Proterro	Genetically modified cyanobacteria for sugar production	Sucrose	Pilot
6	GlobalBioenergies	Genetically modifies *E. coli* to produce light olefins such as isobutene and butadiene	Isobutene	Pilot
	Myriant Corporation	Biosynthetic production of D(-) lactic and succinic acids by modified *E. coli*	Succinic acid	Demo
	OPX Biotechnologies	Synthetic microbes and bioprocess engineering for biofuels and chemicals	3-HP	Pilot
	Spiber Inc.	Synthetic spider silk for textile applications	Spidersilk	Pilot

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Analysis

Monte Carlo analyses predict when each lab- and pilot-scale startup is most likely to launch its first internally developed product, with some companies ahead and some behind the curve.

Monte Carlo Analyses Stress Test Today's Crop of Lab and Pilot-scale Companies

Now that the landscape analysis provided average values and standard deviations for each key scale-up milestone, we can then take that data and generate Monte Carlo estimates to predict the probability that each of today's youngest companies –those currently at lab scale (see Figure 5) and pilot scale (see Figure 6) – will put out a product in each of the upcoming years. For the scope of this analysis, we will focus on companies that are internally developing routes to BBMC products. Because of this, companies putting out products targeting the food and nutrition markets (e.g., Evolva and its stevia product) and companies that have nearer term routes that were acquired (e.g., Calysta's aquacultural feed route that came from the acquisition of BioProtein) are excluded.

To stress test the companies and predict the peak likelihood for product launch, we conducted a single variable Monte Carlo analysis. Based on a Q-Q plot analysis of the scale-up milestone data from the landscape (see Figure 7), each set of scale-up milestone data exhibits a fairly normal distribution, therefore the Monte Carlo analysis leveraged a random number generator with a normal distribution to generate the values that served as the basis for the calculations.

For this report, the Monte Carlo analysis took the start year for a company or its project and added the time it would take the startup to launch its first product. The time it would take to launch its first product was the target variable for the Monte Carlo analysis and was generated 10,000 times using a random number generator with a normal distribution having an average of 7.42 years and a standard deviation of 2.91 years, which corresponded to the industry average determined in the landscape. From there, the data was analyzed to determine the probability that a company would enter the market in each year from 2010 to 2030. In the following sections, we forecast long-term then near-term product launches, and then identify companies behind the commercialization curve.

For the Youngest Startups, First Products Are Most Likely to Be Launched from 2017 to 2022

For those companies that have most recently started working on their synbio platforms, the Monte Carlo analysis estimates these companies are most likely to commercialize their first internally developed BBMC products between 2017 and 2022 (see Figure 8). Falling into this bucket are young, lab-scale startups like Industrial Microbes and pilot-scale companies like Nucelis.

- **Ambercycle recently started up, leaving lots to do before it launches its recycling technology.** Founded in 2013, Ambercycle is one of the youngest startups analyzed and modifies *E. coli* to produce enzymes capable of breaking down polyethylene terephthalate (PET) so the terephthalic acid (TPA) monomer can be recovered. The company's target business model is to source waste PET, such as disposable beverage containers and PET fibers, degrade them in-house, and sell the resulting TPA. This requires the company to not only scale up the enzyme production technology, but also the PET recycling technology. The current management team does not have all the critical experience needed to fully scale and deploy the approach; however, with a peak likelihood of a first product launch in 2020 to 2021, the company still has ample time to grow and bring in the required knowledge base.
- **Ascenix Biotechnologies is still in the lab, despite previous attempt to raise money and scale.** Ascenix Biotechnologies spun out of the University of Minnesota to not only produce isobutyric acid, but also convert isobutyrate to methylmethacrylate via chemical. Though the company is still at lab scale, it still has until 2020

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Figure 7: Q-Q Plot to Test forNormalcy

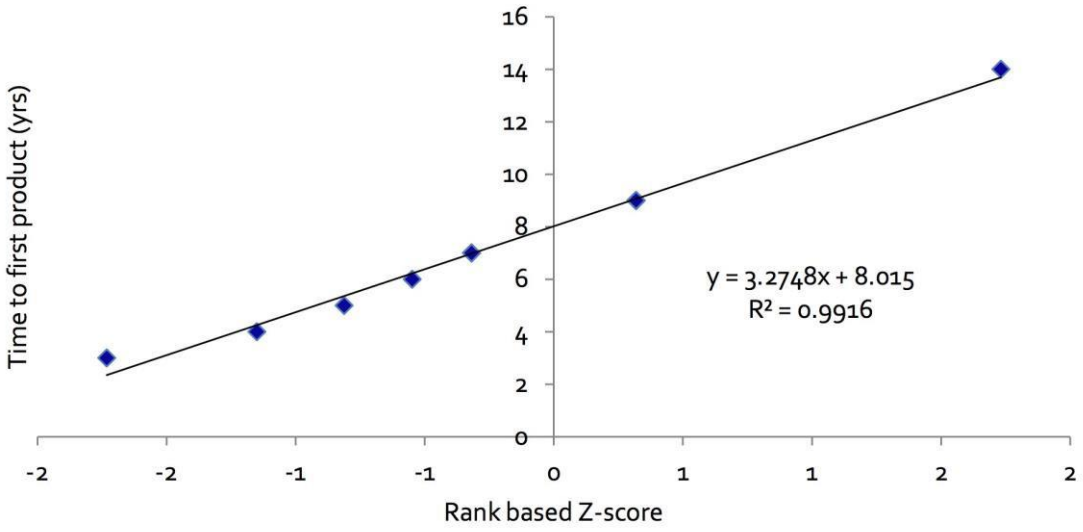
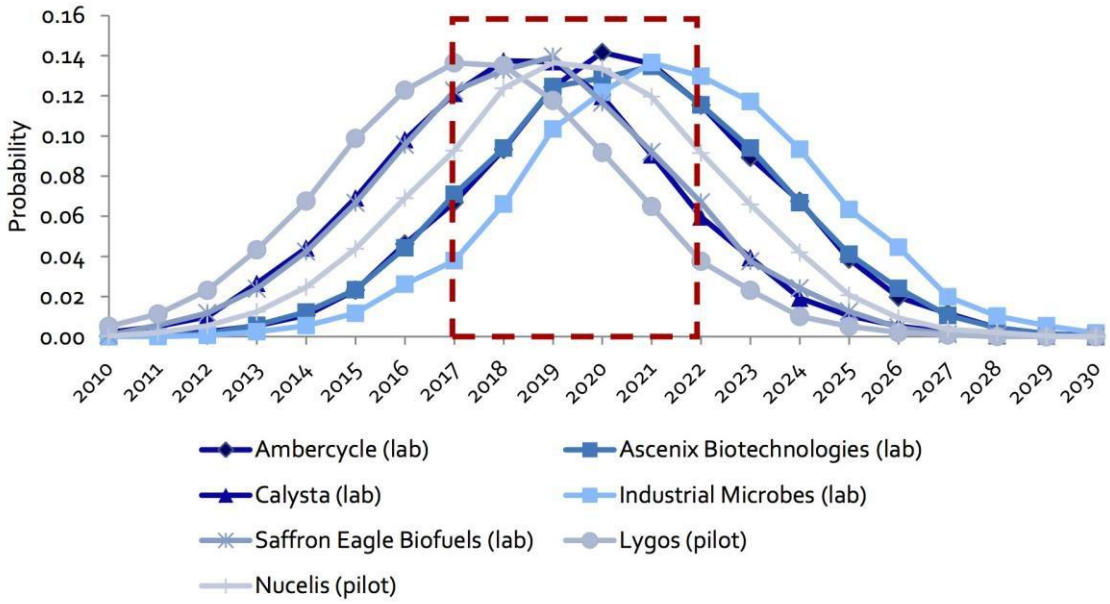


Figure 8: Companies Predicted to Most Likely Release Their First Product between 2017 and 2022



to 2021 to put out a first product before it falls behind the industry average. When we last spoke with the CEO, William Faulkner, in May 2013, the company looked to raise $3 million, part of which would be used to perform pilot-scale research. However, the company is still at lab scale today, nearly two years later. Though the company still has five or so years to put out a product before it falls behind the industry average, the missed scale-up milestone is concerning and clients looking to engage should dig further into the company's current status and plan for movingforward.

- **Calysta claims multiple routes ahead of lactic acid, but this is the first announced internal one.** Calysta is a unique case; therefore, clients are advised to use an extra layer of consideration when using the Monte Carlo analysis as part of their assessments. As previously mentioned, the Monte Carlo analysis is focused on the lactic acid route; however, that is not the company's most advanced pathway. Not only did the company acquire a commercially ready aquacultural feed technology, it also claims to have other, undisclosed pathways that are further along than the publically announced lactic acid platform. However, the methodology will still allow some prediction of when this product may hit the market. If this product follows the same average scale-up timelines as its companions in the bio-based space, then Calysta is most likely to put out its lactic acid product between 2018 and 2019. However, as this is not the company's primary commercialization focus and may not even be its secondary focus, clients are cautioned that the timelines for Calysta are less firm than they are for other companies with a primary commercialization focus of spinning out an internally developed BBMC product. While it's possible that Calysta will go the route of other companies, such as Reverdia and Nucelis, and put out a product quickly by relying on past experience, it is also possible that Calysta's focus is pulled away from lactic acid and the pathway languishes.

- **Industrial Microbes has the longest ramp for its peak likeliness of product launch.** Industrial Microbes began as a paper study back in 2013 and started wet lab work in 2014, making it the youngest company analyzed here. The company is developing the technology to produce malic acid from CO_2 and natural gas via microbial fermentation and is predicted to have a peak likeliness for product launch in 2021 to 2022. The company still has many questions to address and needs to prove out the value of its technology at scale, but it is still too early to call if the company will meet or even beat the industry average with such a long ramp to go.

- **Saffron Eagle Biofuels' past troubles cast doubt over its ability to launch a product.** Despite the fact that Biofuels is part of the company's name, Saffron Eagle Biofuels is actually primarily focused on producing thermoplastic additives and isopentanol. With a peak likeliness of product launch in 2018 to 2019, the company still has a few years to see if it can achieve market launch. That said, the company experienced a key setback when its plans to retrofit a U.S. corn ethanol facility were halted due to the change in focus and financial struggles of its undisclosed Indian partner funding the project. This resulted in the company halting the commercialization of its isopentanol process, which now casts a cloud of doubt over whether or not the company will be able to launch a product at all. Clients interested in engaging should note that the thermoplastic additive technology still at the lab scale and the company needs to demonstrate it can lock down the partnerships and funding required to scale and deploy its approach.

- **Lygos aims to hit demonstration scale in 2015, putting it on track with the industry average.** Since its founding in 2010, Lygos has focused on developing a process to produce malonic acid from acid-tolerant yeast. The company achieved pilot scale in 2014 and has a predicted peak likeliness of product launch in 2017 to 2018. For clients interested in engaging or monitoring Lygos, the next key milestone to look for is production at demonstration scale, something the company aims to do by the end of 2015. Though there is still some work to be done before a product launch, achieving demonstration scale in 2015 will still leave the company with a few years to launch a product or hit commercial scale before falling behind of the industry's average.

- **Nucelis aims to break the mold and put out a product well ahead of its industry peers.** Nucelis spun out of its parent, Cibus, and then was taken back as a wholly owned affiliate (see the January 9, 2014 LRMCJ). Despite the bounce – and potential red flags one may infer – the company is actually setting itself up to beat out the industry product launch average by a good margin. When we spoke with Nucelis president Sean O'Connor in March 2015, Sean said the company aims to launch its first product, squalane in Q4 2015. It then intends to launch its second product, vitamin D2, in 2016. According to the average product launch timelines for the industry, Nucelis' peak likeliness of product launch is 2019 to 2020 – a successful product launch in 2015 would certainly put Nucelis ahead of the game. Clients interested in either squalane or Vitamin D2 offtake are encouraged to engage, as the company is working with toll manufacturers and can tailor volume production to customer demand.

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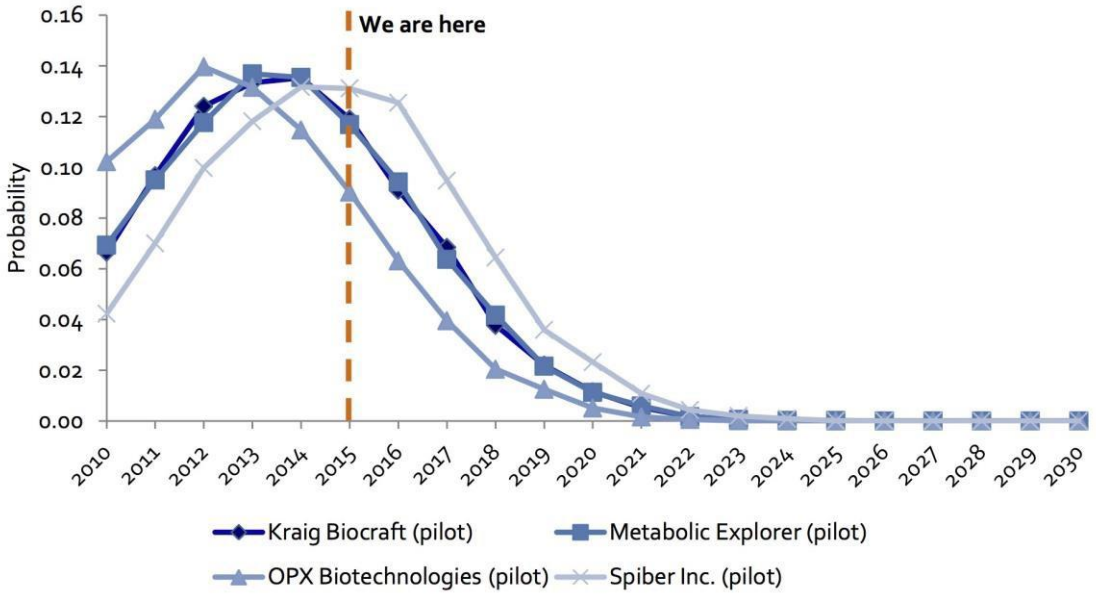
Figure 10: Companies Predicted to Most Likely Release Their First Product Prior to 2015



translate into commercial successes. In our recent conversation with OPX, CEO Michael Rosenberg said the company is no longer working with Dow Chemical on its bio-acrylic acid project and is targeting its first 3-HP outlicense in 2018, one year after the target commercialization of its fatty acid platform. If this was a one off instance, the commercialization likelihood at OPX wouldn't look so dire. However, the company has a history of missed milestones, funding delays, and layoffs. Unless it successfully achieves its goal of raising $10 million to $30 million by the end of this year, clients are advised to only engage with OPX to acquire IP or assets.

- **Spiber Inc may be behind the industry's average, but it is keeping up its forward momentum.** Based in Japan, Spiber Inc is another startup focused on the production of spider silk. In this instance, though, the company is using *E. coli* and other host organisms to produce the synthetic spider silk proteins, which will then be weaved into fibers targeting textiles, automotive markets, and medical applications. Based on this Monte Carlo analysis, the company was predicted to have a peak likeliness for a product launch between 2014 and 2015. Though the company is slightly behind the industry average, it is still making progress. In November 2013 the company completed construction of its 100 kg per month prototyping unit, it produced a proof-of-concept cocktail dress in June 2013, and is currently working with Kojima Industries to build a plant with a capacity of 10 tpa. This larger facility is targeting production by the end of 2015 and clients are advised to closely monitor not only the progress on this facility, but also whether or not it can meet the cost targets necessary for commodity textile and automotive markets.

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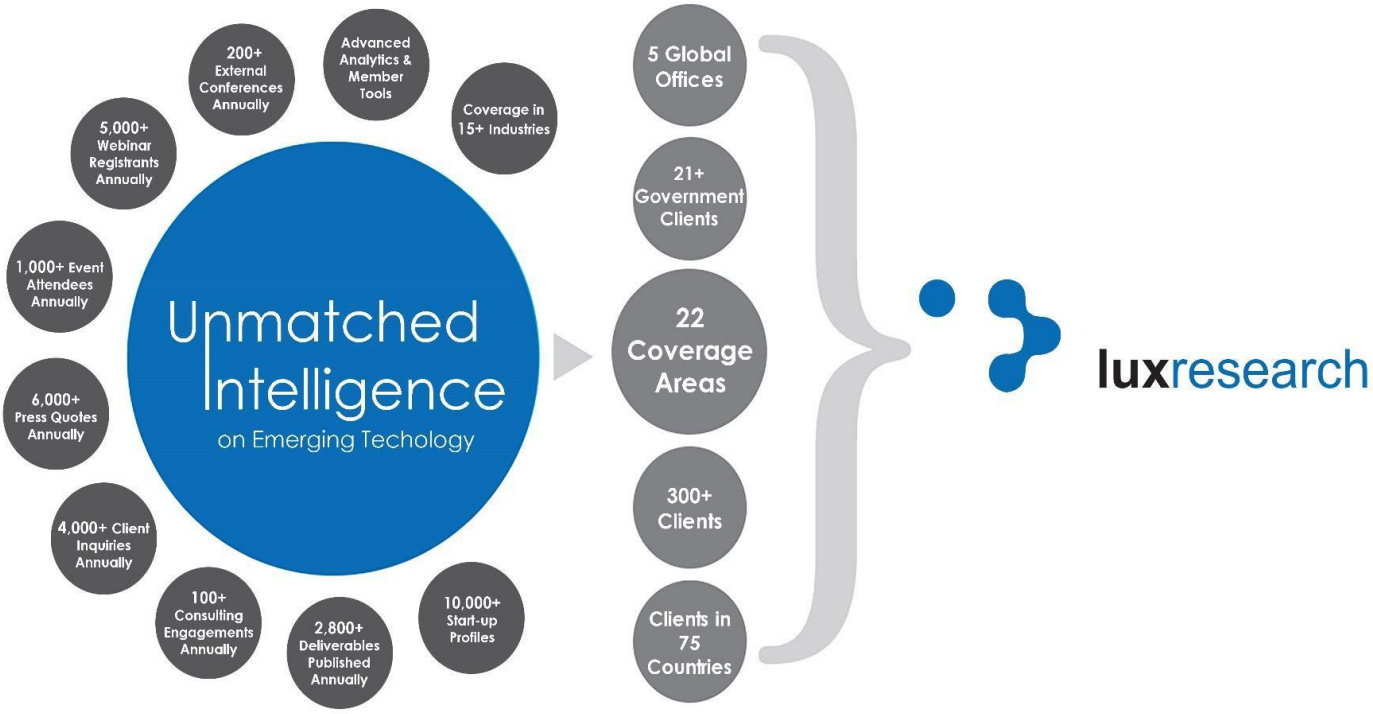

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